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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

AKHAVAN, RAMIN

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 08/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/844,508

Applicant(s)

WOLFFE ET AL.

Examiner

Ramin (Ray) Akhavan

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 May 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6, 8, 10-13, 17-33 and 43-70 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6, 8, 10-13, 17-33 and 43-70 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

An amendment filed 05/28/2004 is acknowledged. Claims 1 and 43 have been amended, and claims 1-6, 8, 10-13, 17-33 and 43-70 are pending and under consideration in this action. Any objections or rejections not repeated herein are hereby withdrawn. Where applicable, Applicant's arguments with respect to rejections maintained will be addressed in the body of the rejection. New grounds for rejection being set forth herein (*Infra*, Obviousness Double Patenting) are necessitated by discovery of a co-pending Continuation In Part application (App. No. 10/084,826), which has inventors in common with instant application. Applicants will not be permitted to extend the prosecution of the present application by failing to provide notice to the Office of the conflicting copending application, the discovery of which necessitated the new grounds of rejection at this advanced stage of prosecution. With appropriate notice, these grounds of rejection could have been incorporated in the prior Office Action. Such a circumstance is clearly analogous to the policy of making an action final where Applicant's material amendments to the claims necessitated a new ground of rejection, since in both instances it is the applicant who caused the rejection to be applied after the case had received an action on the merits. See MPEP § 706.07(a). Additional new grounds of rejection are necessitated by material amendments to the claims, thus **this action is FINAL**.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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- 1. Claims 1-6, 8, 10-13, 17-33 and 43-70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.**

The claim(s) contains subject matter, "fusion molecule does not regulate transcription", which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The amended language introduces a negative limitation into base claims 1 and 43, where the negative limitation constitutes **NEW MATTER**, as there does not appear to be any support for such a limitation in the specification. Applicant points to page 5, lines 9-12 as one example of a passage that supports the negative limitation. However, upon examining the entire specification, including the cited passage, there does not appear to be any support for this negative limitation. Indeed, that chromatin modification can enable transcription is contemplated, not excluded. For example, in the very passage that Applicant cites, the disclosure reads, "These compositions and methods are useful for facilitating processes that depend upon access of cellular DNA sequences to DNA-binding molecules, for example, transcription, replication, recombination, repair and integration". (Spec. p. 5, ll. 9-12; *See also*, p. 51, ll. 10-12, 19-27; p. 52, ll. 10-13). Therefore, the claims are rejected for containing new matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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- 2. Claims 1-6, 8, 10-13, 17-33 and 43-70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* modification of chromatin, does not reasonably provide enablement for *in vivo* use.**

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The test for enablement is whether one skilled in the art could make use the claimed invention from the disclosure in the specification coupled with information known in the art without undue experimentation. *United States v Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor but instead is a conclusion reached by weighing many factors which are outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). The factors include the following:

Scope/Breadth of the claims. The broadest claims read on a method of altering any cell's chromatin structure, thus read on both *in vitro* and *in vivo* application of the invention(i.e. altering chromatin structure). The chromatin structure in a cell reads on *in vivo* use, which necessarily reads on *any* organism. More limiting embodiments are directed to chromatin modification in *any* animals, including humans, as well as plants. Thus the scope of the claimed invention is broad.

Nature of the invention. The invention is drawn to a method of altering *any* cell's chromatin structure by using a fusion protein with a targeting component (i.e. zinc finger DNA binding domain) and a component consisting of at least one subunit with a chromatin remodeling function. Therefore, the invention is drawn to either *in vitro* or *in vivo* use. Furthermore, to the

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extent that the invention is drawn to *in vivo* use, the invention is necessarily directed to gene therapy (e.g. altering DNA expression patterns), because whether the fusion protein is administered through a gene altering or non-gene altering vector (e.g. viral or liposomes), the method is directed to accessing chromatin in the nucleus of the cell. Thus whether applicant intends or does not intend, *in vivo* transcription (i.e. gene expression) is modified through chromatin alteration. The only disclosed utility for such *in vivo* embodiments is for therapeutic effect as well as gene therapy. (e.g. Spec. p. 48, ll. 1-15; p. 51, ll. 18-21; p. 52, ll. 22-26; p. 56, ll. 19-22).

State of the art/ Unpredictability of the art. With respect to *in vivo* chromatin structure modification, “[C]hromatin in mammalian cells remains relatively poorly understood...due to...the complexity of the chromatin remodeling machinery, and the dynamic properties of chromatin *in vivo*.” (Urnov et al. EMBO rep. 2002; 3(7) :610-15, at 610, Abstract). Notably, the primary thrust of the work in the art is directed to regulation of gene expression, perhaps because the chromatin remodeling machineries, whether involved in transcription, replication or DNA repair are physically and functionally linked. (Morales et al. Biochimie, 2001; 83(11-12) :1029-39, at 1038). Moreover, even with respect to remodeling complexes where subunits have been somewhat characterized viz., function, “Many questions remain regarding the specific functions of these subunits, their organization with the complexes, and how they work together to accomplish their task”. (Wang, W. Curr. Top. Microbiol. Immunol., 2003; 274:143-69, at 156). In sum the state of art with regard to characterization of complexes, their subunits and their affects/function *in vivo* is in the early stages of development, with the

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salient point being that there remains a great deal of unpredictability with respect to *in vivo* use for chromatin remodeling.

In addition, in regard to *in vivo* modification of chromatin structure, based on the state of the art, it would highly unpredictable whether a fusion construct once administered to an animal, would first, evade the immune system, and second, not impart unintended deleterious effects (e.g. toxicity or remodeling non-target sites). For example, as the functionality for the many subunits of the many multi-protein remodeling complexes remains to be elucidated, there is a small degree of predictability. In addition, functionality *in vitro* does not necessarily translate into functionality *in vivo*, commensurate with the scope of the claims.

In addition, as the invention is broadly drawn to any remodeling complex, be it those that either function as motors to disrupt nucleosomes (e.g. ATP-driven) or as enzymatic machinery to modify histones chemically (e.g. acetylases and deacetylases), there would be a heightened degree of unpredictability, because each complex functions through distinctly different mechanism. Furthermore, each mechanism could be part of a complex system of pathways involved in different cellular processes (e.g. replication or DNA repair), where introduction of applicant's fusion protein may disrupt pathways in an unintended way or in unintended target cells/tissue so as to have unpredictable effects. Thus while the intended purpose *in vivo* would be to provide access to DNA (i.e. remodel chromatin) for one purpose, an unintended downstream outcome might result, such as modifying expression of an unintended target gene. With respect to certain mechanisms of chromatin remodeling, for example, such as ATP-driven remodeling complexes, it is not known how or by what mechanism chromatin is remodeled, thus there is greater unpredictability for *in vivo* applications; "[T]he mechanistic basis for how

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[remodeler] SWI/SNF uses the energy of ATP hydrolysis to alter nucleosome structure has remained a major unsolved mystery.” (Peterson and Workman. *Curr. Opin. Genet. Dev.* 2000; 10(2):187-92, at 187).

With respect to unpredictability in gene therapy, the art is still a highly unpredictable area within biology and medicine. For example, vectors used to deliver fusion constructs encoding therapeutic products may be erroneously inserted into a particular gene resulting in unknown, adverse or detrimental effects. (See, Check, Erika, Feb. 13, 2003, *Nature*, 421: 678) (citing occurrence of leukemia due to insertion of retroviral vectors used in gene therapy into a particular stretch of DNA); (See also, Juengst, ET. June 2003, *BMJ*, 326:1410-11) (indicating that gene transfer often has multiple and unpredictable effects on cells).

Amount of guidance provided. There is guidance provided with respect to making the fusion constructs. Aside from prophetic generic suggestions on gene transfer methods (e.g., Spec. pp. 38-39), there is little guidance on how to use the invention, a process of altering chromatin structure *in vivo* whether using gene transfer or administration of fusion proteins directly. For there to be sufficient guidance, the disclosure would have to teach how to deliver the fusion protein *in vivo* to circumvent potential toxicity, an adverse immune response, as well as potential unintended targeting (e.g. activating non-target chromatin containing non-target genes), only in so far as such concerns contribute to unpredictability of using the invention *in vivo*.

Number of working examples. All examples provided are *in vitro* (e.g. HeLA cells and 293 cells).

Amount of Experimentation Required. The level of skill in the art required to practice the claimed invention is high. Given the unsolved hurdles to successful practicing of the invention, the level of unpredictability in the art and lack of working examples, it must be considered that the skilled artisan would be required to conduct trial and error experimentation of an undue nature in order to attempt to practice the claimed invention commensurate with the scope of the claims.

Response to Arguments

Applicant's arguments with respect to obviating the scope of enablement rejection are not deemed persuasive. Applicant's assertions can be summarized as directed to claim's not reading on gene therapy, that determinations of safety or efficacy are irrelevant, that working examples are never required to establish enablement, that the cited references do not establish unpredictability.

As noted above (under Scope/Breadth of the Claims and Nature of the Invention) the claims are enormously broad, directed to chromatin modification in virtually *any* organism. Applicant asserts that the claims simply do not read on gene therapy and further, the claims do not require that gene expression be altered. In addition, Applicant asserts that there are multiple disclosed utilities *in vivo* for the claimed methods/proteins that do not require gene therapy or altering of gene expression. However, in so far as the claims are not limited in any way with respect to altering chromatin structure, further in light of what is disclosed in the specification, the fusion protein must be delivered to cells *in vivo*. For example, the therapeutically effective amounts of fusion polypeptide or a nucleic acid encoding a fusion polypeptide must be injected

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into the organism or delivered via a retrovirus, for example. (e.g. Spec. p. 48). Thus, the claims *do* read on gene therapy, based on their breadth and the disclosed embodiments in the specification. In addition, even if Applicant had taught how to deliver the vectors/proteins into the nucleus of target cells *in vivo*, which they have not, once chromatin is modified the endogenous cellular factors (e.g. transcription factors) could have access to the DNA. Therefore, whether the claims require it or not, one consequence of modifying chromatin is that transcription of genes will be altered. This is clearly pointed out in Applicant's own disclosure, as well as the above cited art.

Applicant's next assertion is that issues of safety and efficacy are irrelevant with respect to whether a disclosure meets the enablement requirement. Applicant is correct that the proper test is whether one of skill could make and use the invention from the disclosure coupled with information known in the art without undue experimentation. More particularly, Applicant asserts that safety/efficacy concerns do not weigh on patentability and should be left for other government agency. However, what Applicant fails to recognize is that the safety and efficacy issues weigh in on the unpredictability of using the claimed invention *in vivo*. Correlatively, while generally it may not be an absolute requirement that *in vivo* examples are provided, the fact that no relevant examples are provided, again weighs in on the unpredictability of using the claimed invention *in vivo*. Applicant's sole argument as support for the disclosure enabling *use* is that delivery vectors/methods are described. (Remarks, p. 14, ¶ 2; citing Spec. pp. 49-51). Given the complexity of the invention and the breadth of the claims, mere prophetic recitation of how pharmaceuticals are to be delivered or what are various gene transfer vectors, is not deemed to teach to one of skill how to *use* the invention. The safety and efficacy concerns are not

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dispositive in and of themselves, but only weigh on the unpredictability of using the invention *in vivo*. In addition, that working examples are not provided is, as required, weighed on whole with other *Wands* factors, in light of what is known in the art. Therefore, the presence or absence of examples relating to modification of chromatin structure *in vivo* is certainly relevant to the enablement inquiry, given that specification only provided prophetic guidance as to how to use the invention *in vivo*. Applicant also contends, with respect to whether claimed constructs/proteins could evade the immune system of an organism, that many mammalian remodeling complexes have been disclosed. (Remarks, p. 16, Note 4). This does nothing to discount the immune system issue, as the fusion proteins or nucleic acids, whether mammalian or not, would be recognized as foreign by any given organism with an intact immune system. Moreover, that certain embodiments within the scope of the claimed invention may be enabled (i.e. *in vitro*) does not necessarily obviate a scope of enablement rejection.

Finally, Applicant asserts that the cited references do not establish unpredictability, because the cited references are silent as to fusion molecules as claimed. (Remarks, p. 16, ¶ 2 middle). As stated above, the state of art with respect to *in vivo* chromatin remodeling is underdeveloped with many answers yet to be discovered. Applicant contends that the references cited provide discussions about chromatin remodeling or chromatin structure and do not rise to the level of establishing unpredictability. The cited references show that chromatin remodeling *in vivo* is at a nascent stage of development and that many questions remain with respect to protein complexes or subunits involved in remodeling. (*Supra*, Wang, W. 2003, at p. 56). That such questions remain in conjunction with the safety/efficacy concerns cited herein and in light of the lack of any relevant guidance or *in vivo* examples, in sum, indicate a great deal of

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unpredictability. In addition, in regard to gene therapy, Applicant asserts that fusion molecules that do not remodel chromatin are not encompassed by the claims. If an embodiment for the broadly claimed invention encompasses delivering the construct encoding the fusion protein via a retroviral vector, then fusion molecules that do not effectuate the intended outcome (i.e. inserting into non-target sites), *are* encompassed by the claims. Based on the foregoing, on whole, one of skill would be required to undertake undue experimentation to practice the claimed invention *in vivo*, thus the rejection is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

- 3. Claims 1-6, 8, 10-13, 17-33 and 43-70 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-33 and 44-71 of copending Application No. 10/084,826.**

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

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Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to biologically and patentably indistinguishable subject matter. In fact, but for semantic differences the reference claims anticipate thus necessarily make obvious the instant claims. For example, instant base claims 1 and 43 recite, "A method for altering a region of interest in cellular chromatin...", compared to reference claim 1 and 44 which recite, "A method for modifying a region of interest in cellular chromatin...". Dependant claims are written with identical language (e.g. instant claims 18-23 and reference claims 18-23). Therefore, but for the patentably indistinguishable language in the base claims, the claims are drawn to indistinguishable subject matter.

Conclusion

No claims are allowed. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,


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however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ramin (Ray) Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached on Monday- Friday from 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


GERRY LEFFERS
PRIMARY EXAMINER